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Original Research Article

Scientific Validation of *Desmodium gangeticum* Bioactive for Effective Management of Pancreatitis: *In-silico* Molecular Docking

Rishikesh Kumar Tiwari[1*], Jitender K Malik[1]

[1]Faculty of Pharmacy, P.K. University, Shivpuri (M.P.)-India

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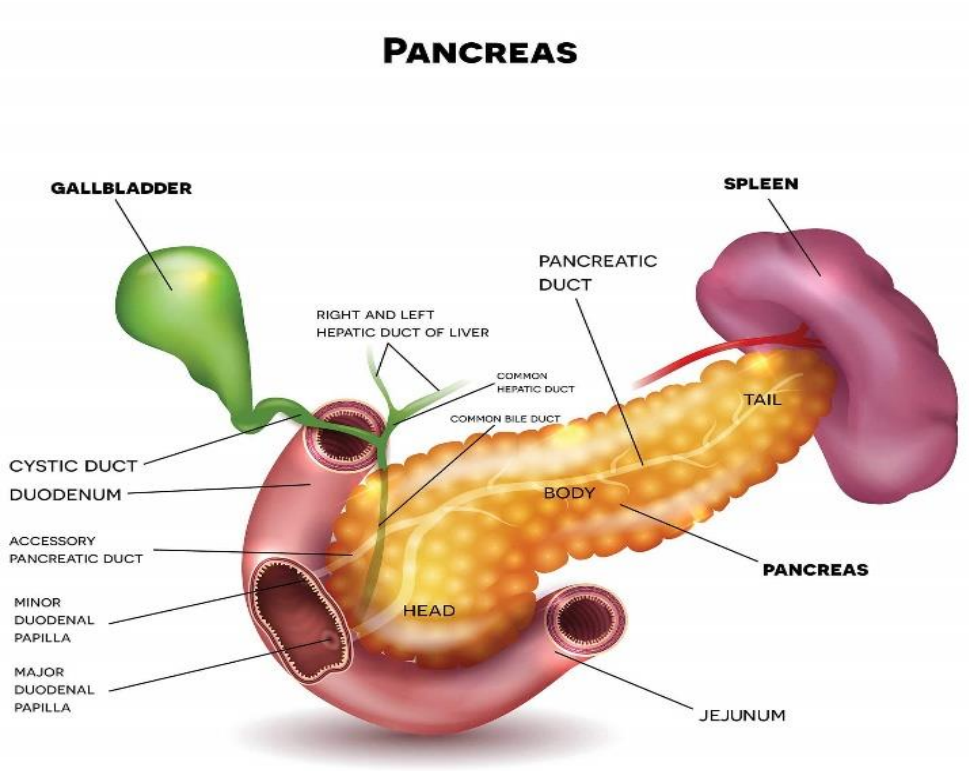
Abstract: ***Background*:** The pancreas becomes inflamed when someone has pancreatitis. When the digestive enzymes are triggered before they are released into the small intestine and start targeting the pancreas, pancreatic injury results. Pancreatitis comes in two different flavours: acute and chronic. Gallstones and alcohol use are two of the many factors that can cause pancreatitis. Pancreatitis can be treated well with medicinal plants. Desmodium gangeticum (DC), a plant of the Fabaceae family, is also known as salpan, salvan, and sarivan in Hindi. The plant is bitter, sweet, thermogenic, nervine tonic, aphrodisiac, carminative, constipating, diuretic, febrifuge, cardiotonic, anticholinestrase action, anti-inflammatory, and expectorant, and it is highly beneficial in treating a variety of medical conditions. ***Method*:** In the current work, *NF-kβ* receptor inhibitors were sought after using a molecular docking approach. The binding was determined by the Auto Dock software utilizing a grid-based docking method. Compounds' 2D structures were constructed using the chem sketch, converted to 3D, and then energetically reduced up to an arms gradient of 0.01. (MMFF). ***Result*:** *D.gangeticum* found to be effective anti-pancreatitis agent and their lead molecules (daidzein and genistein)effectively binds to be target protein *NF-kβ* receptor with binding energy -5.99 & -5.81 kcalmol^{-1} for daidzein & genistein respectively. ***Conclusion*:** It was discovered through a computationally based docking analysis that both lead compounds exhibit strong *NF-KB* receptor inhibiting effects. The results demonstrated a promising docking score and lead molecule's pattern of binding to the target protein's active region with strong covalent bonding. The synergistic impact of daidzein and genistein is what gives aqueous extract from *D gangeticum* its ability to heal pancreatitis.

Keywords: Pancreatitis, molecular docking, daidzein and genistein.

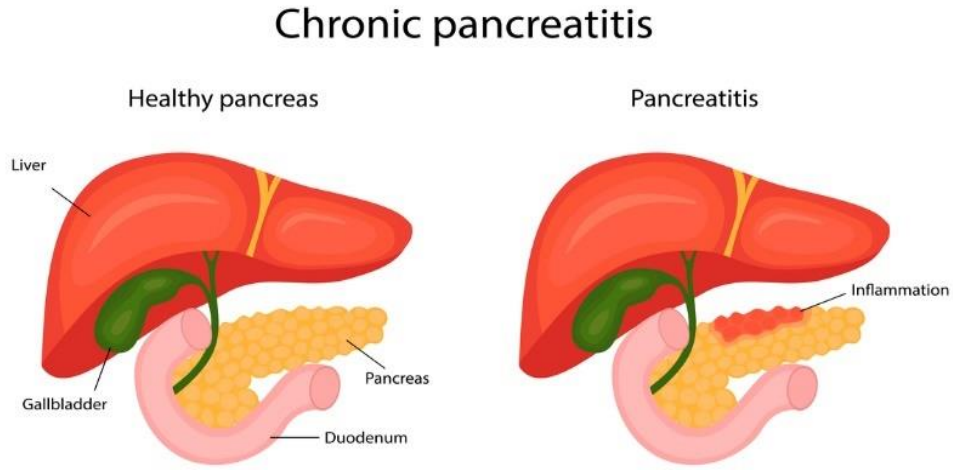
INTRODUCTION

About 6 inches long, the pancreas is located behind the stomach across the rear of the belly. The pancreatic duct, a tiny tube that connects the pancreas' head to the duodenum, the first segment of the small intestine, is located on the right side of the abdomen. The pancreas' tail, or narrow end, reaches to the left side of the body [1]. A sizable gland located behind the stomach and close to the small intestine is the pancreas. There are two primary things the pancreas does. It helps with food digestion by releasing potent digestive enzymes into the small intestine. It causes the bloodstream to release the hormones glucagon and insulin. The body employs these hormones to regulate how it uses food for energy.

***Corresponding Author:** Rishikesh Kumar Tiwari
Faculty of Pharmacy, P.K. University, Shivpuri (M.P.)-India



The pancreas becomes inflamed when someone has pancreatitis. When the digestive enzymes are triggered before they are released into the small intestine and start targeting the pancreas, pancreatic injury results. Pancreatitis comes in two different flavours: acute and chronic. An intracellular stimulation of pancreatic digesting enzymes results in acute pancreatitis, a pancreatic inflammatory condition. With the release of cytokines and reactive oxygen metabolites, the destruction of pancreatic parenchyma causes a systemic activation of the coagulation, kinin, complement, and fibrinolytic cascades. If this is severe and overwhelming, shock, acute renal failure, and the acute respiratory distress syndrome may result. Cholelithiasis is a contributing factor in about 45 percent of instances, and alcohol addiction affects an additional 35 percent of patients. 10% of patients may have no known causes. Acute pancreatitis can cause significant tissue damage, cyst formation, infection, and bleeding into the pancreatic gland in extreme situations. Other crucial organs like the heart, lungs, and kidneys can also suffer damage from severe pancreatitis [2, 3].



Pancreatitis

Symptoms of Pancreatitis	
Acute pancreatitis	**Chronic pancreatitis**
Upper abdominal pain, Abdominal pain that radiates to your back, Abdominal pain that feels worse after eating, Fever, Rapid pulse, Nausea, Vomiting, Tenderness when touching the abdomen	Upper abdominal pain, Losing weight without trying & Oily, smelly stools (steatorrhea).

The pharmacological activity of medicinal plants is frequently understood as a result of millennia of trial and error, but they need to be thoroughly explored if we want to create new drugs that fit the standards of contemporary treatment. Man has used diverse plant parts for both the treatment and prevention of many illnesses since the dawn of time. In the past, plants were the source of all therapeutic remedies, whether they were in the straightforward form of plant parts or in the more sophisticated form of crude extracts, mixes, etc. Today, many medications that are effective against a variety of ailments are made from plants. The bulk of these entail the extraction and subsequent alteration of the active ingredient (chemical compound) present in a certain medicinal plant. The use of medicinal plants is widespread among the indigenous people in rural parts of many developing countries, while 25% of medical medications in developed countries are based on plants and their derivatives [4].

Desmodium gangeticum (DC), a plant of the Fabaceae family, is also known as salpan, salvan, and sarivan in Hindi.

List of phytoconstituents [5]

S. No	Chemical Classes	Phytoconstituents	Uses
1	Flavanoids	Genistein and 2- hydroxygenistien, 8-C-Prenyl-5, 7, 5'-trimethoxy-3, 4'-methylenedioxyflavone.	Bronchitis, cough,
2	Flavonoid glycoside	4,5,7-Trihydroxy-8-prenylfavone-4-O-α-L-rhamnopyaronosyl-(1-6)β-D- glucopyranoids	
3	Pterocarpanods	Gangetin, gangetinin, desmodin and desmocarpin.	Antibacterial, Anti-fertility activity.
4	Lipids and glycolipids	Aminoglucosyl glycolipids and cerebroside.	Antioxidant activity.
5	Alkaloids	Tryptemines. Phenetylamines, tryptamine –N- Oxide, Phenetylamine-N-Oxide, N-Ndimethyltryptamine, N-N-dimethyltryptamine-N-Oxide, 5-Methoxy-N-N dimethyltryptamine, indole-3-alkylamine and β-carboline, Caffeic acid and chlorogenic acid	Antiemitic, antiamnesic, Antibacterial activity.

Desmodium gangeticum (L.) DC. is well known in India for its bitter tonic, febrifuge, digestive, anti-emetic, antipyretic, and anti-catarrhal properties. Neurological diseases are also commonly treated with it in Ayurveda. *Desmodium gangeticum* plant's aqueous extract possesses potent anti-writhing and mildly CNS depressing properties. Gallstones, renal calculi, and bladder calculi are all treated with a decoction of the leaves in Java [6, 7].

Experimental work

***In-Silico* Molecular docking studies**

Ligand Preparation:

2D Structure of ligands like daidzein and genistein were drawn using ChemSketch [8], the two-dimensional structures of the prepared ligands were converted into their 3-D structures optimized with 3D geometry. The optimized structures were saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligands were given below:

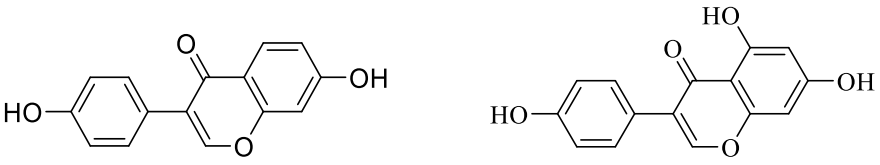


Figure 1: 2D structure of daidzein and genistein

Preparation of the grid file

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing and grid points is given in table 1 [9-11].

Table 1. Grid parameters used in current docking analysis of NF-KB

S. No.	Receptor	x-axis	y-axis	z-axis	Spacing	x center	y center	z center
1	NF-KB	48	58	58	0.394	28.358	17.443	43.771

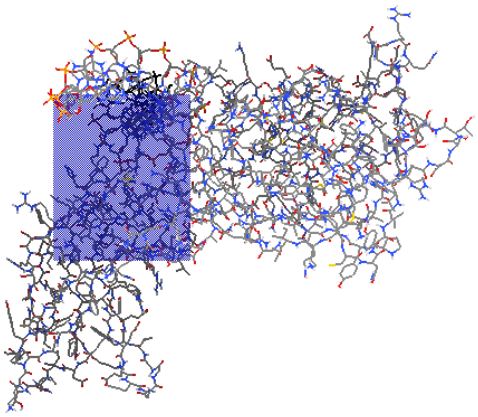


Figure 2: Grid box covering all active sites in NF-KB receptor

Preparation of the docking file

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [12-15].

Docking Study

Crystal structure

The crystal structure of the protein consisting of NF-KB receptor is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (1svc.pdb) registered in the Protein data bank was used [16-17]. The complex ligand was separated by using Chimera software.

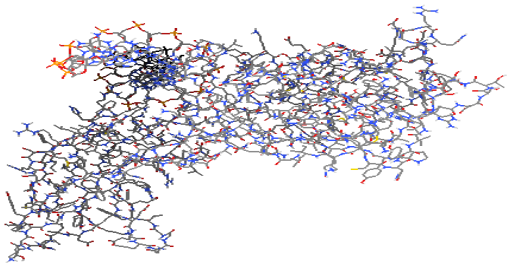


Figure 3: Crystal structure of NF-KB receptor (PDB ID-1svc)

Processing of Protein

The downloaded receptor protein is having only one chains, i.e. chain A, which has been selected for experimental purpose and complex ligand was removed from it. The bound ligand was separated from the macromolecular complex by using software Chimera [18].

Molecular Docking Simulation Studies

Docking of ligands like daidzein and genistein against NF-KB receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [19].

Toxicity & ADME-T Studies

The ligand molecules viz. daidzein and genistein were studied by online program OSIRIS, for

prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [20-22].

RESULT & DISCUSSION

The incidence of acute pancreatitis (AP) is increasing globally and mortality could be high among patients with organ failure and infected necrosis. The predominant factors responsible for the morbidity and mortality of AP are systemic inflammatory response syndrome and multiorgan dysfunction. Therefore scientific validation for assessment of anti-pancreatitis activity was done by computational based molecular docking study of lead molecules of *D.gangeticum* against *NF-kβ* receptor.

Several years of experimental studies have implicated nuclear factor-kappa B (NF-κB) activation as an early and central event in the progression of inflammation in AP. As per Jakkampudi A etal;2016 NF-κB, being a central molecule that links the initial acinar injury to systemic inflammation and perpetuate the inflammation [21].

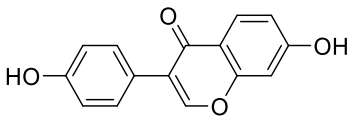
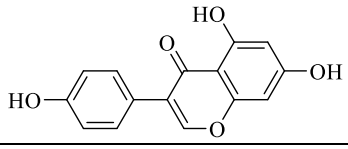
It has been investigated whether a range of medicinal plants could serve as potential sources of medications that treat pancreatitis. We performed an *in-silico* screening of the phytoconstituents daidzein and genistein on *NF-kβ* receptor.

D.gangeticum found to be effective anti-pancreatitis agent and their lead molecules effectively binds to be target protein *NF-kβ* receptor with binding energy -5.99 & -5.81 kcalmol^{-1} for daidzein & genistein respectively. The result was tabulated in table 2. The binding mode of selected lead molecules showed in fig.4-5. The 2D and 3D interaction of selected compound displayed in fig.6-11. The interaction of daidzein & genistein with active site at *NF-kβ* receptor showed as follows:

Compound	Conventional Hydrogen bounding	Pi-sigma bounding	Covalent bounding	Week Vander's interaction
Daidzein	LYS^{80}, HIS^{67}, ARG^{59}, ARG^{57}	PHE ^{56}	PRO^{71}	GLY^{60}, SER^{81}, GLY^{55}
Genistein	LYS^{80}, ARG^{57}, ARG59, GLY69	PRO^{71}	PHE^{56}	SER^{81}, GLY^{68}, HIS^{67}

The pharmacokinetic profile reveals that it is having good pharmacokinetic profile but with the presence of any major toxic effects including mutagenicity, tumorogenicity and reproductive effects. Theoretically, both the ligand molecules have shown encouraging docking score.

Table 2: Results of docking of ligands like daidzein and genistein against NF-KB receptor

Sl. No	Compound Name	Structure	Binding Energy (Kcal/mole)
1	Daidzein		-5.99
2	Genistein		-5.81

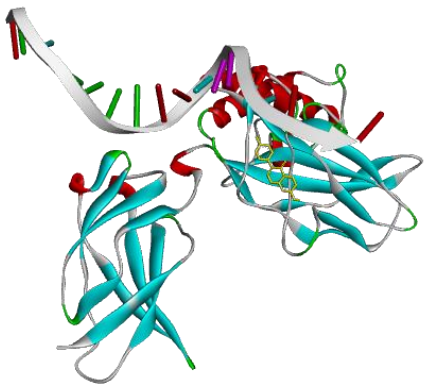


Figure 4: Binding mode of daidzein within the active site of NF-KB receptor

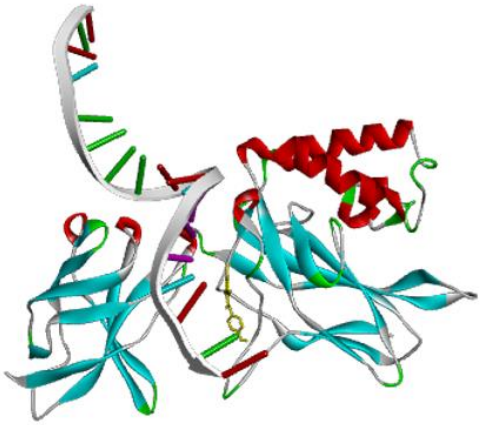


Figure 5: Binding mode of genistein within the active site of NF-KB receptor

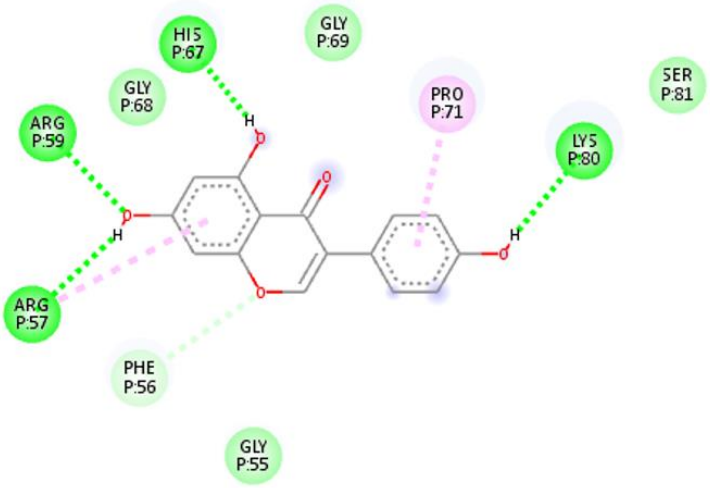


Figure 6: Two-dimensional binding mode of daidzein within the active site of NF-KB receptor

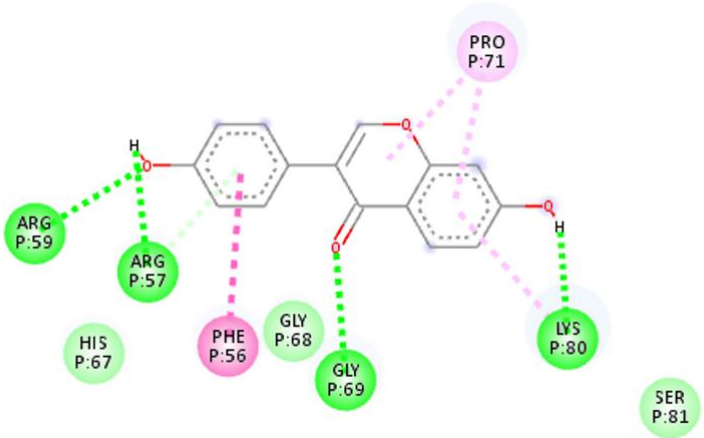


Figure 7: Two-dimensional binding mode of genistein within the active site of NF-KB receptor

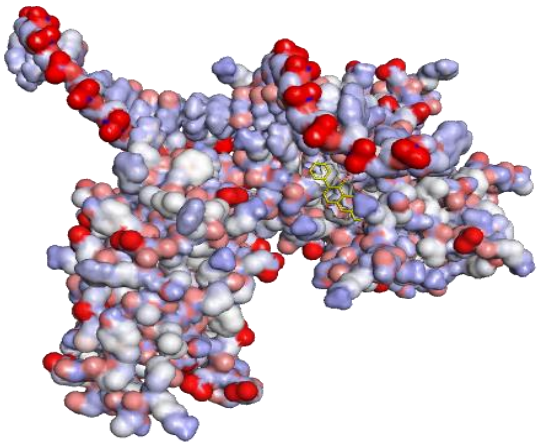


Figure 8: Three-dimensional binding conformation of daidzein within the active site of NF-KB receptor

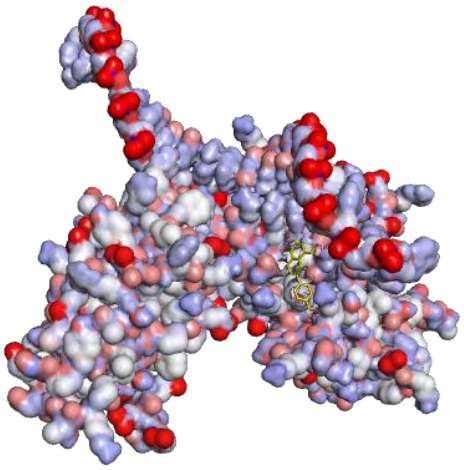


Figure 9: Three-dimensional binding conformation of genistein within the active site of NF-KB receptor

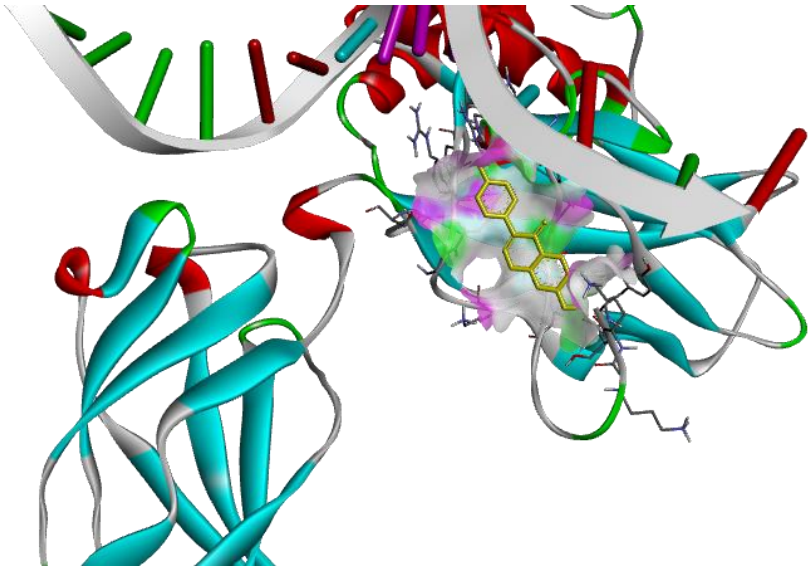


Figure 10: Three-dimensional binding mode of daidzein within the active site of NF-KB receptor

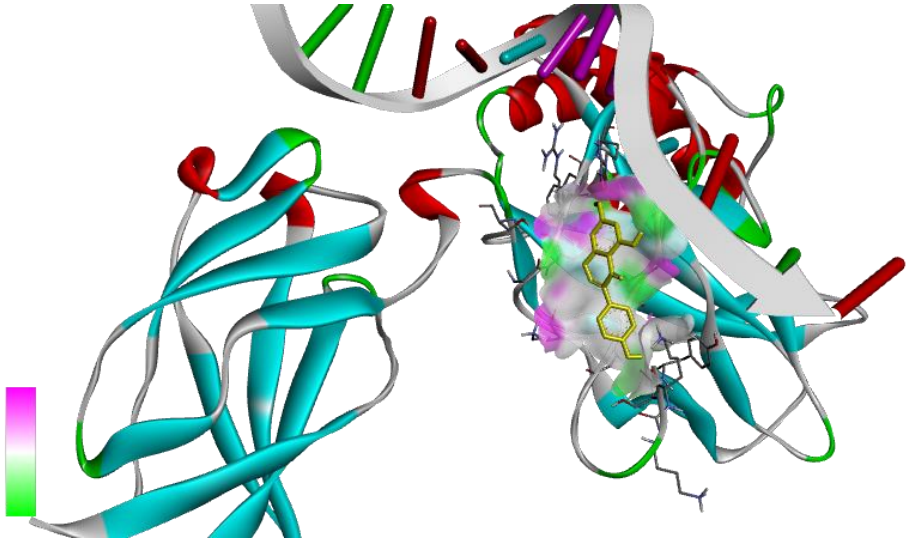


Figure 11: Three-dimensional binding mode of genistein within the active site of NF-KB receptor

CONCLUSION

Flavonoid like daidzein, genistein, rutin and quercetin found in aqueous extract from *D gangeticum* as per literature survey. As a result, daidzein and genistein were chosen as the lead compounds for the *in-silico* validation investigation.

Because proinflammatory cytokines like tumour necrosis factor-a (TNFa) and interleukin-1 (IL-1) activate NF-kB and NF-kB is involved in the expression of other proinflammatory genes like cytokines, chemokines, and adhesion molecules, it has long been assumed that NF-kB is the prototypical proinflammatory signalling pathway. Numerous studies have shown additional flavonoids such epicatechin, fisetin, genistein, and naringin to be protective against pancreatitis-induced beta cell degeneration. The reduction of oxidative stress and subsequent prevention of DNA damage and the caspase cascade are two major molecular mechanisms by which flavonoids promote beta cell survival. By boosting both enzymatic (catalase, glutathione peroxidase, glutathione S transferase, superoxide dismutase) and non-enzymatic (reduced glutathione), flavonoids increase the antioxidant capacity of beta cells. Beta cells are shielded from autophagy, apoptosis, and necroptosis as a result of the increased antioxidant ability, which prevents ROS buildup and lipid peroxidation.

It was discovered through a computationally based docking analysis that both lead compounds exhibit strong *NF-KB* receptor inhibiting effects. The results demonstrated a promising docking score and lead molecule's pattern of binding to the target protein's active region with strong covalent bonding. The synergistic impact of daidzein and genistein is what gives aqueous extract from *D gangeticum* its ability to heal pancreatitis.

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